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Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors†

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SUMMARY

Purpose—To assess spontaneous reports of rhabdomyolysis associated with simvastatin (SV) and pravastatin (PV) for evidence of CYP3A4 interaction. Clinical trial results advocate cholesterol lowering in high-risk patients including diabetics and the elderly. Given the association between advancing age, metabolic, and cardiovascular disease, many patients are treated with concomitant medications upon statin initiation. Although statins are generally safe, minor and severe adverse reactions arise, especially when given to patients taking concomitant medications that inhibit the statin clearance and lead to increased statin plasma concentration.

Methods—We conducted a comparative case series of rhabdomyolysis reports associated with SV and PV. Domestic spontaneous reports were obtained from the FDA's Adverse Event Reporting System (AERS). Drug utilization data were obtained from IMS HEALTH and the National Ambulatory Medical Care Survey (NAMCS). Adverse event reporting rates (AER) and ratios (AERR) of rhabdomyolysis associated with SV and PV—with and without stratification by CYP3A4 inhibitor concomitancy were determined.

Results—Stratification by CYP3A4 inhibitor concomitancy did not change the rhabdomyolysis AER for PV with or without a CYP3A4 inhibitor (2.4 cases and 3.1 cases per 10 million Rx, respectively). However, stratification of SV reports with or without a concomitant CYP3A4 inhibitor resulted in a rhabdomyolysis AER (38.4 and 6.0 cases per 10 million Rx, respectively). The corresponding AERR with or without a CYP3A4 inhibitor were 0.77 for PV and 6.43 for SV.

Conclusions—Spontaneous adverse event reports provide evidence of increased risk for rhabdomyolysis based on interaction between SV and selected CYP3A4 inhibitors.

†There was no conflict of interest.

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DISCLAIMER

The views expressed are those of the authors and do not necessarily represent those of the Food and Drug Administration or imply its endorsement.

Keywords

rhabdomyolysis; statins; CYP3A4 inhibitors; HMG-CoA reductase inhibitors; adverse reactions; interaction; spontaneous reports

INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are extremely effective in the treatment of dyslipidemias.¹ They are well tolerated by the vast majority of patients, but are infrequently associated with muscle related toxicity on a continuum from minor myalgias to potentially fatal rhabdomyolysis.² Though rare, rhabdomyolysis has been reportedly associated with all currently marketed statins. Post-marketing reports of rhabdomyolysis resulted in the suspension of cerivastatin (CV) marketing, likely due to a drug–drug interaction.³ However, because statins have variable physiochemical properties, certain statins may be more or less likely to interact with concomitant medications.

Due to high affinity and selectivity for the HMG-CoA reductase enzyme, statins have little potential to alter the pharmacokinetics of other drugs.⁴ However, the unique pharmacokinetic (PK) characteristics of each statin may substantially impact their susceptibility to be modified by concomitant medications.⁵ The PK differences between statins include: solubility, phase I and II metabolism, utilization of hepatic transporters, formation of active metabolites, bioavailability, protein binding, and excretion. Importantly, simvastatin (SV) and lovastatin (LV) are administered as lactone pro-drugs while the other statins are administered as β -hydroxy acids. SV and LV lactone undergo hydrolysis in the plasma, intestinal mucosa, and liver to form active β -hydroxy acids.^{6–10} One PK characteristic shared by all statins is extensive first pass hepatic extraction.

Hepatic extraction occurs by two primary mechanisms—active transport and passive diffusion. Organic anion transporting polypeptide (OATP) is the primary membrane protein which actively transports hydrophilic statins pravastatin (PV) and rosuvastatin (RV) from portal circulation into the hepatocyte (influx). The lipophilic statins atorvastatin (AV), CV, fluvastatin (FV), LV and SV enter mainly by passive diffusion; however, the acid forms of these statins also utilize active transport.^{5,11–14}

Following entry into the hepatocyte each statin undergoes a unique cascade of metabolic and non-metabolic processes which ultimately results in cholesterol biosynthesis inhibition and statin elimination. The metabolic processes include phase I oxidation (mediated by cytochrome P450 (CYP) isoenzymes) and phase II glucuronidation (mediated by UDP glucuronosyl transferase (UGT)). The CYP isoenzymes responsible for phase I statin metabolism are 3A4, 2C8, 2C9, and 2C19. AV, LV, and SV are oxidized by the CYP3A4 isoenzyme to form both active and inactive metabolites.^{15,16} CV is oxidized by CYP2C8 and to a lesser extent CYP3A4.¹⁷ FV is oxidized by CYP2C9.^{13,17} PV has no phase I metabolism and is minimally metabolized by phase II glucuronidation. RV also has negligible phase I metabolism (by CYP2C9 and CYP2C19) and is primarily eliminated as the unchanged parent compound.^{10,18}

Following hepatocyte entry and metabolism (phase I and II), statins exert their cholesterol inhibitory effect and are subsequently eliminated. However, a varying proportion of statin reaches systemic circulation, by efflux transport and passive diffusion.^{5,11,12} The efflux transport proteins: P-glycoprotein (P-gp) and multi-drug resistance associated protein 2 (MRP2), are believed to affect the disposition, bioavailability, and elimination of all statins—primarily in the acid form.¹⁹ For most statins, elimination occurs through biliary

excretion; however, PV is partially eliminated by renal excretion. Inhibition of statin metabolism (phase I or II) and/or active membrane transport (influx or efflux) may result in elevated statin concentrations and has the potential to increase the risk for statin related adverse events.

Gemfibrozil (GEM) and cyclosporine (CSA) have been shown to interact with statins *via* both metabolic and hepatic transport pathways. Shitara *et al.*²⁰ showed the drug interaction between GEM and CV occurred *via* inhibition of CV hepatic uptake (*via* OATP) and oxidation (*via* CYP2C8). Similarly, CSA was shown to inhibit hepatic uptake (OATP), efflux transport (P-gp and MRP2), and oxidation (*via* CYP3A4).²¹ Olbricht *et al.* showed a 5- and 20-fold increase in area under the curve (AUC) for PV and LV respectively in kidney transplant patients treated with CSA.²² Given PV is not a CYP3A4 substrate, the increased AUC is the likely result of transporter mediated inhibition.

This investigation focuses on statin phase I metabolic inhibition, specifically the drug interaction between statins and concomitant drugs which inhibit CYP3A4 mediated metabolism (CYP3A4 inhibitors). As serious statin adverse events are dose and plasma concentration related, it is recognized that plasma levels of statins oxidized by the CYP3A4 isoenzyme may increase when these statins are concomitantly administered with CYP3A4 inhibitors.^{15,23,24} Many commonly used pharmaceuticals are CYP3A4 inhibitors.²⁵ Drug classes that include CYP3A4 inhibitors are calcium channel blockers, antibiotics, antifungals, antidepressants, antiretrovirals, and immunosuppressants.²⁵

The CYP3A4 isoenzyme metabolizes more than 50% of marketed drugs.²⁶ A recent investigation showed 25% of new statin initiators received a concomitant CYP3A4 inhibitor in the first year of statin therapy.²⁷ Case reports, risk-factor models, and clinical trials have shown concomitant administration of statins and CYP3A4 inhibitors may increase the risk for rhabdomyolysis.²⁸⁻³⁰ Because of the potential increased risk, some statin product labels warn against concomitant administration with CYP3A4 inhibitors.

To study the clinical impact of this association we studied two statins with different phase I metabolism, but similar hepatic transport mechanisms. SV (a CYP3A4 substrate) was chosen as the object drug and PV (a non-CYP3A4 substrate) as the comparator object drug. While the phase I metabolic pathways for SV and PV are different, both statins should be similarly impacted by influx and efflux hepatic transporters (*via* OATP, P-gp, and MRP2).^{31,32} Based on published reports by Hsiang *et al.*¹¹ and Chen¹⁹ *et al.* it is believed that hepatic transport (influx and efflux) of SV acid and PV are equally involved. Any transporter inhibition, due to co-administration of a CYP3A4 inhibitor (e.g., CSA), should impact transporter mediated shunting of SV acid and PV similarly.

Studies to quantify the hazard of rhabdomyolysis for different statins (with different metabolism) with CYP3A4 inhibitor concomitancy have not been conducted. The purpose of this investigation is to study spontaneous reports of rhabdomyolysis associated with SV and PV to determine if the CYP3A4 mediated drug interaction results in a selective increase in rhabdomyolysis reporting rates based on different statin metabolic pathways. Given the aforementioned physiochemical characteristics of each statin, we hypothesized an increased risk for SV, but not for PV, with CYP3A4 inhibitor concomitancy.

METHODS

Study design

We conducted a comparative case series of spontaneous reports of rhabdomyolysis associated with PV and SV to assess interaction with selected CYP3A4 inhibitors. To

control for population exposure to each statin, we used the estimated total number of PV and SV prescriptions as denominators for each case group.

Case source

This analysis was conducted at the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). Cases consisted of domestic (U.S.) spontaneous adverse event reports of rhabdomyolysis associated with PV and SV. These reports were submitted to the FDA by pharmaceutical manufacturers or health care professionals through the MedWatch program. MedWatch reports are archived in CDER's Adverse Events Reporting System (AERS) database and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). A concise review of the history and treatment of adverse drug event reports at CDER, including epidemiological inference, has been reviewed separately.³³

Case definition

Reports of rhabdomyolysis associated with PV and SV were obtained from the AERS database. We acquired all cases of rhabdomyolysis associated with these two agents from market launch (November 1991 for PV; January 1992 for SV) through July 2001. The cut-off date of July 2001 was selected to limit the effect of stimulated rhabdomyolysis reporting following the suspension of CV marketing in August 2001. Reports were selected using the MedDRA terms *rhabdomyolysis*, *myopathy*, or *myalgia* with further restriction for rhabdomyolysis that required hospitalization. After identification of putative cases, all reports were manually reviewed by the authors (C.R., A.B.).

A case of rhabdomyolysis was defined as a patient with a health care professional (HCP) diagnosis of rhabdomyolysis or a HCP diagnosis of myositis or myopathy with a creatine phosphokinase (CPK) > 10 000 IU/L. Exclusion criteria included non-U.S. reports, non-HCP reports, duplicate reports, "hearsay" reports, published reports, and cases with a history of: non-statin related rhabdomyolysis, myositis, dermatomyositis, renal transplantation, or HIV infection/treatment. In order to reduce confounding by concomitant statin-fibrate exposure, reports listing concurrent use of GEM were excluded from the primary analysis, but were included in a secondary analysis.

Case exposure definition

Each report was carefully reviewed for specific mention of recent administration of PV or SV and a concomitant CYP3A4 inhibitor. We further verified the temporality of the statin alone or the statin-CYP3A4 inhibitor concomitancy to the event date. We required both the statin and the CYP3A4 inhibitor to be listed (within 30 days of each other) in either the concomitant medications section or specific mention of a concomitant (statin-CYP3A4 inhibitor) therapy in the narrative. Additionally, we required documentation of the statin-CYP3A4 inhibitor concomitancy to be no more than 30 days prior to the event date *or* specific mention of close temporal association between concomitant exposure and the event in the narrative.

The CYP3A4 inhibitors chosen for this investigation were: CSA, clarithromycin, erythromycin, diltiazem, verapamil, mibefradil, itraconazole, ketoconazole, fluconazole, nefazodone, and fluvoxamine. Despite our attempt to study CYP3A4 inhibitors known for potent and selective CYP3A4 inhibition, some of the selected CYP3A4 inhibitors also inhibit other metabolic and hepatic transport pathways.

Population exposure source

Drug utilization data were acquired for the purpose of estimating total U.S. exposure to PV and SV with and without a CYP3A4 inhibitor during the study period (denominator data). These data were acquired from two different sources—IMS HEALTH National Prescription Audit Plus (NPA Plus) and NAMCS. NPA Plus data were used to estimate the total number PV and SV prescriptions dispensed in the United States from late 1991 through July 2001.³⁴ The concomitant statin-CYP3A4 inhibitor frequency was determined using NAMCS.

NAMCS is a national probability sample survey of office-based physicians conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. Statistics derived from NAMCS are representative of all ambulatory care visits to physicians engaged in non-federal, office-based health care. Participating physicians agree to systematic sampling and review (*via* chart abstraction) of patient visits during a randomly selected week of the year. For the sampled visits, the physician provides details of specific patient information including patient demographics, reason for the visit, up to three medical diagnoses, treatments, and disposition. New and continued prescriptions are recorded as well as other treatments and recommendations. Data gathered from this survey are transcribed into standard international classification of diseases (ICD-9) nomenclature. Concomitancy data for PV and SV with a CYP3A4 inhibitor were collected from NAMCS during the time period 1993–2001. NAMCS is a practical source to estimate statin-CYP3A4 concomitancy, although it may not be representative of the overall United States concomitant frequency distribution.

In order to calculate the number of statin prescriptions with a concomitant CYP3A4 inhibitor, we multiplied the total number of PV and SV prescriptions by the concomitant frequency proportion for PV and SV with a CYP3A4 inhibitor. The remainder of each calculation is the total number of PV and SV prescriptions without a CYP3A4 inhibitor.

Measures of effect

The adverse event reporting rate (AER), measured as cases per 10 million prescriptions, will be calculated using the actual number of cases of rhabdomyolysis associated with either PV or SV (as the numerator) and the estimated population exposure as the denominator. The adverse event reporting rate ratio (AERR) will also be calculated to reveal the relative effect for each statin with and without a concomitant CYP3A4 inhibitor.

The primary analysis consisted of calculating the rhabdomyolysis AER and AERR associated with PV and SV stratified by the presence or absence of a CYP3A4 inhibitor. Secondary analyses were conducted to evaluate the potential impact of statin dose and to compare the rhabdomyolysis AER and AERR with statin-GEM concomitancy.

RESULTS

Characteristics of cases

A search of the AERS database MedWatch reports from 1991 through July 2001, recovered 73 and 321 potential cases of rhabdomyolysis associated with PV and SV respectively. Following hands-on review, 25 and 118 reports, for PV and SV respectively, were classified as unique cases fitting the case definition. Demographic and clinical characteristics of these cases are shown in Table 1. The median age for both groups was 66 years. Fifty-five per cent and 44% of the reports were for female patients for PV and SV, respectively. The median reported time to onset of rhabdomyolysis was 8 months for PV and 5.5 months for SV. A switch from one statin to another statin within 60 days of the event was reported in one out of 25 (4%) PV cases and 11 out of 118 (9%) SV cases. Five (20%) PV and 25 (21%)

SV treated patients reported acute renal failure or required dialysis. Four patients reportedly died from events presumably related to the adverse drug reaction (two (8%) patients treated with PV and two (2%) treated with SV).

Among the 25 PV and 118 SV associated cases, three (12%) and 56 (47%) reported a concomitant CYP3A4 inhibitor, respectively. The distribution of PV and SV cases with a concomitant CYP3A4 inhibitor is shown in Table 2. Of interest, six cases associated with SV and one case associated with PV reported two concomitant CYP3A4 inhibitors.

Table 3 shows the SV and PV dose analysis stratified by concomitant CYP3A4 inhibitor. Importantly, the median SV dose with and without a concomitant CYP3A4 inhibitor was equivalent (40 mg). However, the mean SV dose was higher (56 mg vs. 38mg) for cases reporting a concomitant CYP3A4 inhibitor than for cases not reporting a concomitant CYP3A4 inhibitor. A similar dose analysis for PV cases was not possible due to missing dose information among the three PV cases reporting a concomitant CYP3A4 inhibitor. A recent dose increase was reported in 0 out of 25(0%) PV cases and 23 out of 118 (19%) SV cases.

Reporting rate analysis

The NPA Plus audit produced 83 673 000 and 120 188 000 U.S. dispensed retail prescriptions for PV and SV from initial marketing.³⁴ The observed range of physician response for NAMCS was 63% (1999) to 73% (1993). Table 4 shows the NAMCS concomitant frequency data for selected CYP3A4 inhibitors and GEM. The proportion of mentions of PV and SV with a concomitant CYP3A4 inhibitor was 0.1526 and 0.1231 respectively. For use in the secondary analysis, the proportion of concomitant mentions of PV and SV with concomitant GEM was 0.0079 and 0.0149 respectively. Based on these data, we found the estimated U.S. population exposure for PV and SV to be approximately 83 million and 118.4 million U.S. dispensed prescriptions (without GEM concomitancy). The primary analysis will use these two numbers for calculating the AER and AERR.

Table 5a shows the unadjusted AER analysis for PV and SV. Twenty five cases of rhabdomyolysis associated with PV were identified among an estimated 83 million PV prescriptions yielding an AER of 3.0 cases per 10 million prescriptions. One hundred eighteen cases of rhabdomyolysis associated with SV among an estimated 118.4 million SV prescriptions yielding an AER of 10.0 cases per 10 million prescriptions. Without adjusting for CYP3A4 inhibitor concomitancy, the rhabdomyolysis AERR (SV/PV) was 3.3.

AERs and AERRs stratified by concomitant use of CYP3A4 inhibitors are shown in Table 5b. The AERs for PV with and without a concomitant CYP3A4 inhibitor are 2.4 and 3.1 cases per 10 million prescriptions (AERR = 0.77). The AERs for SV with and without a concomitant CYP3A4 inhibitor are 38.4 and 6.0 cases per 10 million prescriptions (AERR = 6.43). Table 5b also shows the relative effect of SV cases to PV cases. When stratified by CYP3A4 inhibitor, the relative effect (AERR) of SV/PV is 16.0 (38.4/2.4) and 1.9 (6.0/3.1) with and without a CYP3A4 inhibitor, respectively.

Tables 6a and b show the secondary analysis with concomitant statin and GEM. Twenty eight PV and 159 SV spontaneous reports of rhabdomyolysis met the pre-specified inclusion criteria. Among these cases, 3 PV and 41 SV cases reported concomitant exposure to GEM. The unadjusted AERs were 3.3 and 13.2 per 10 million prescriptions for PV and SV, respectively. Stratifying the PV cases by concomitant GEM gave AERs of 3 and 45 per 10 million prescriptions with and without GEM respectively (AERR = 15). Stratifying the SV cases by concomitant GEM gave AERs of 229 and 10 per 10 million prescriptions with and without GEM respectively (AERR = 23).

All results use the aggregate proportion of all CYP3A4 inhibitors with a concomitant statin (SV = 0.1526, PV = 0.1231). However, individual CYP3A4 inhibitor concomitancy with SV resulted in AER point estimates greater than the baseline AER (6.0 cases per 10 million SV Rxs without a CYP3A4 inhibitor) (data not shown).

DISCUSSION

This descriptive analysis of rhabdomyolysis AERs and AERRs associated with PV and SV reveals noteworthy effect modification by CYP3A4 inhibitor concomitancy for SV but not PV. The unadjusted AERs and AERRs for SV and PV are consistent with previous findings. Chang *et al.*³⁴ reported a crude reporting rate ratio of 4 (SV/PV), which approximates our unadjusted AERR of 3.3 (SV/PV). Contrasting the baseline AERR with the stratified AERR (by CYP3A4 inhibitor concomitancy) suggests a striking interaction which may reflect different PK clearance pathways for PV and SV.

In order to further explore the phase I interaction hypothesis, we conducted a secondary analysis among PV and SV reports with concomitant GEM as the interacting drug. GEM has been shown to inhibit phase I metabolism (*via* primarily the CYP2C8 isoenzyme), phase II metabolism (glucuronidation) and uptake transport (*via* OATP).²⁰ In contrast to CYP3A4 inhibitors, GEM minimally inhibits the phase I metabolic pathway for either PV or SV. Thus, we hypothesized no effect modification for PV and SV with concomitant GEM. Supporting this hypothesis, the results show that although PV-GEM and SV-GEM concomitancy is associated with elevated AERs (Table 6b), the relative effect (AERR) is seemingly non-differential between PV (AERR = 15) and SV (AERR = 23) with *versus* without GEM.

The statin-GEM findings provide another level of evidence to support the effect modification found in the primary analysis. While GEM exhibited interaction potential with CV plausibly through both metabolic (CYP2C8) and uptake transport (OATP) pathways, it does not possess PK characteristics that make it likely to differentially interact with PV or SV. Although both PV and SV rely on hepatic uptake transport *via* OATP, neither drug undergoes phase I metabolism by CYP2C8. Thus, the non-differential finding with concomitant GEM is expected and reassuring.

As shown in Table 3, stratification by statin dose provides inconclusive results for SV and PV associated rhabdomyolysis when adjusted for a concomitant CYP3A4 inhibitor. Despite skewed data with large variances, SV-associated cases have the same median dose regardless of CYP3A4 concomitancy. However, for PV cases, it is not possible to compare the impact of increasing dose between the two strata due to missing dose information for cases reporting CYP3A4 concomitancy. Further analyses need to be conducted to fully evaluate the potential interaction by statin dose given missing and inconsistent data inherent to voluntary, spontaneous reports.

Although the findings from this study are consistent with a robust and selective interaction between SV and CYP3A4 inhibitors, the study has limitations which should be highlighted. Spontaneous AERs are believed to significantly underestimate actual incidence rates. This occurs because the adverse event must be: diagnosed, attributed to a drug, reported to the FDA or to the manufacturer, and documented with specific information in order to meet study inclusion criteria. Furthermore, the discrepancy between reporting rates and incidence rates may increase as physicians become more comfortable identifying and managing statin-related side effects.

Other limitations involve the quality of case reports. Although the MedWatch form has changed little during the study period, the content of each case report may differ considerably from report to report. This difference is further complicated by the reporting source, e.g., pharmaceutical manufacturer or health care provider. In order to improve study precision, we excluded cases reported by non-health care providers and recorded the reporting source as a potential confounding variable. Fortunately, there was near perfect balance of reports reported to the FDA by the pharmaceutical manufacturers for SV and PV. However, this does not rule out differential protocols for managing adverse event reporting between the manufacturers.

Further limitations should be considered regarding the drug utilization estimates (the denominator used in calculating reporting rates). This is particularly true for the proportion of concomitant CYP3A4 inhibitor therapy with PV (0.15) and SV (0.12). These concomitant frequency proportions were derived from NAMCS, a weighted and projected annual national survey of approximately 2000 office-based physicians in the U.S. There may be substantial variability for infrequent events—such as infrequently used drug products. This variability is therefore increased in the assessment of coincident events, such as the concomitant use of two specific agents (e.g., a rarely used drug product in conjunction with a statin).

Furthermore, NAMCS may not capture drugs prescribed by non-NAMCS participating physicians, particularly specialists. Section 9 requests information on “medications that were ordered, supplied, administered or continued during this visit.” As this statement is subject to interpretation, one practice may record all patients medications while another may record only those ordered, supplied, administered, or continued during that specific office visit. For example, if a NAMCS participating primary care physician records the statin therapy he initiated (or refilled), but does not record the antifungal therapy prescribed by a dermatologist, the concomitancy therapy is not recorded. This potential inconsistency may underestimate the true proportion of concomitant statin-CYP3A4 inhibitor therapy. Underestimating concomitancy (statin-CYP3A4 inhibitor or statin-GEM concomitancy) would overestimate the reporting rates and reporting rate ratios. To better understand the impact of a potential underestimation of the proportion of statin-CYP3A4 inhibitor concomitancy, we conducted a sensitivity analysis for different proportions of statin-CYP3A4 inhibitor concomitancy. Table 7 shows an inverse relationship between the concomitant frequency proportion and the AERs and AERRs. That is, if the concomitancy estimate is underestimated, the reporting rates and reporting rate ratios may be biased.

Despite these limitations, our findings are consistent with increased risk of rhabdomyolysis during concomitant use of SV, a CYP3A4 substrate statin, and a CYP3A4 inhibitor. Additionally, the results support observations regarding muscle toxicity in SV clinical trials with concomitant CYP3A4 inhibitors. Further analytic research is warranted to fully elucidate these findings.

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KEY POINTS

- We studied spontaneous reports of rhabdomyolysis associated SV, a CYP3A4 substrate, and PV, a non-CYP3A4 substrate, for evidence of CYP3A4 interaction.
- We found 3 out of 25 PV reports and 56 out of 118 SV reports were associated with a concomitant CYP3A4 inhibitor
- Fifteen per cent of PV and 12.5% of SV prescriptions were concomitantly prescribed with a CYP3A inhibitor.
- The AERRs for rhabdomyolysis (statin w/CYP3A4 inhibitor vs. statin w/o CYP3A4 inhibitor) were 0.77 and 6.34 for PV and SV respectively.
- The comparison of reporting rate ratios (SV/PV) suggests effect modification by CYP3A4 inhibitor as predicted in FDA approved labeling for SV.

Table 1

Demographic and clinical attributes of domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin*

Case attributes	Pravastatin (n = 25)	Simvastatin (n = 118)
Age (years)	n = 16	n = 102
Range	24–79	27–93
Median	66	66
Mean	61	64
Sex	n = 22	n = 110
Female	12	48
Male	10	62
Unknown	3	8
Weight (lbs)	n = 5	n = 48
Mean	171	181
Median	181	173
Reported statin switch	n = 25	n = 118
Number switched (%)	1	11
Concomitant meds	n = 14	n = 106
Median number	5	4
Standard deviation	3	3
Reaction onset (months)	n = 15	n = 82
Range	0.2–33	0.1–90
Median	8	5.5
Mean	12	13
Outcome variables	n = 25	n = 118
Hospitalized	25	118
Death	2	2
CK median	12,300	19 240
CK range	1076–700 000	761–625 333
Acute renal failure or dialysis	5	25
Report characteristics	n = 25	n = 118
Manufacturer report	17	81
Report year (median)	1997	1999
Report year range	1992–2001	1993–2001

* Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions.

Table 2

Domestic spontaneous reports of rhabdomyolysis associated with simvastatin or pravastatin and concomitant CYP3A4 inhibitors

CYP3A4 inhibitor(s)	Number of simvastatin cases	Number of pravastatin cases
Statin plus 1 reported inhibitor		
Clarithromycin	10	
Mibefradil	10	
Verapamil	8	
Nefazodone	6	
Cyclosporine	5	
Diltiazem	5	2
Itraconazole	3	
Erythromycin	2	
Ketoconazole	1	
Statin plus 2 reported inhibitors		
Cyclosporine, diltiazem	1	1
Cyclosporine, itraconazole	1	
Cyclosporine, ketoconazole	1	
Cyclosporine, mibefradil	1	
Cyclosporine, verapamil	1	
Mibefradil, verapamil	1	
Total	56	3

Dose analysis for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin stratified by concomitant use of a selected CYP3A4 inhibitor

Table 3

	All cases		w/ CYP3A4 inhibitor		w/o CYP3A4 inhibitor	
	SV	PV	SV	PV	SV	PV
Reports of rhabdomyolysis	n = 118	n = 25	n = 56	n = 3	n = 62	n = 22
Number reporting dose (%)	95 (80)	13 (52)	46 (82)	0	49 (79)	13 (52)
Dose range (mg)	5–160	20–40	5–160	n/a	5–80	20–40
Mean/median/sd (mg)	47/40/31	26/20/10	56/40/34	n/a	38/40/27	26/20/10
Reported taking max* statin dose (%)	32 (34)	4 (31)	20 (43)	n/a	12 (24)	4 (31)
Recent statin dose increase (%)	23 (19)	0 (0)	13 (23)	n/a	10 (16)	0 (0)

* Max dose refers to the maximum FDA approved dose in the United States (pravastatin = 40 mg; simvastatin = 80 mg).

Table 4

Proportion of concomitant mentions of pravastatin or simvastatin and selected CYP3A4 inhibitors or gemfibrozil in the National Ambulatory Care Survey (NAMCS), 1993–2001

Selected CYP3A4 inhibitors	Pravastatin (%)	Simvastatin (%)
Clarithromycin	0.80	0.01
Erythromycin	0.77	0.19
Cyclosporine	0.52	0.04
Mibefradil	0.06	0.01
Verapamil	5.02	3.80
Diltiazem	8.01	7.53
Nefazodone	0.20	0.27
Itraconazole/ketoconazole	0.28	0.39
Combined total	15.26	12.31
Fibrates		
Gemfibrozil	0.79	1.49

Table 5

a. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin *

	Pravastatin	Simvastatin	AERR
All cases			
Cases of rhabdomyolysis	25	118	
Rxs (1991–2001)	83 012 000	118 397 000	3.3
AER (per 10 ⁷ Rxs)	3.0	10.0	

b. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin stratified by concomitant use of a selected CYP3A4 inhibitor *

	w/CYP3A4 inhibitor	w/o CYP3A4 inhibitor	AERR
Pravastatin cases			
Cases of rhabdomyolysis	3	22	
Rxs (1991–2001)	12 668 000	70 344 000	0.77
AER (per 10 ⁷ Rxs)	2.4	3.1	
Simvastatin cases			
Cases of rhabdomyolysis	56	62	
Rxs (1991–2001)	14 575 000	103 822 000	6.43
AER (per 10 ⁷ Rxs)	38.4	6.0	

* Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions.

Table 6

a. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin *

	Pravastatin	Simvastatin	AERR
All cases			
Cases of rhabdomyolysis	28	159	4
Rxs (1991–2001)	83 673 000	120 188 000	
AER (per 10 ⁷ Rxs)	3.3	13.2	

b. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin stratified by concomitant use of gemfibrozil *

	w/gemfibrozil	w/o gemfibrozil	AERR
Pravastatin cases			
Cases of rhabdomyolysis	3	25	
Rxs (1991–2001)	661 000	83 012 000	15
AER (per 10 ⁷ Rxs)	45.4	3.0	
Simvastatin cases			
Cases of rhabdomyolysis	41	118	
Rxs (1991–2001)	1 791 000	118 397 000	23
AER (per 10 ⁷ Rxs)	228.9	10.0	

* Including cases with concomitant gemfibrozil and gemfibrozil prescriptions.

Table 7

Sensitivity analysis of statin-CYP3A4 inhibitor concomitancy*

Number of prescriptions		Concomitant %	AER [†]		AERR [‡]
w/CYP3A4 inhibitor	w/o CYP3A4 inhibitor		w/ CYP3A4 inhibitor	w/o CYP3A4 inhibitor	
(n = 3)					
(n = 22)					
Pravastatin					
0	83 012 000	0	—	2.7	—
4 150 600	78 861 400	5	7.2	2.8	2.6
8 301 200	74 710 800	10	3.6	2.9	1.2
12 667 631	70 344 369	15.26	2.4	3.1	0.8
16 602 400	66 409 600	20	1.8	3.3	0.5
20 753 000	62 259 000	25	1.4	3.5	0.4
(n = 56)					
(n = 62)					
Simvastatin					
0	118 397 000	0	—	5.2	—
5 919 850	112 477 150	5	94.6	5.5	17.2
11 839 700	106 557 300	10	47.3	5.8	8.1
14 574 671	103 822 329	12.31	38.4	6.0	6.4
17 759 550	100 637 450	15	31.5	6.2	5.1
23 679 400	94 717 600	20	23.6	6.5	3.6
29 599 250	88 797 750	25	18.9	7.0	2.7

*. Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions.

[†] AER is the number of reports/the number of estimated prescriptions (per 10 million prescriptions).

[‡] AERR is calculated as the reporting rate w/a CYP3A4 inhibitor/the reporting rate w/o a CYP3A4.